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Applicant : Gurpreet S. Ahluwalia et al. Art Unit: 1501
Serial No.: 08/963,227 Examiner: R. Harrison
Filed : November 3, 1997
Title : INHIBITION OF HAIR GROWTH

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION OF GURPREET S. AHLUWALIA UNDER 37 C.F.R. § 1.132

I hereby swear:

1. I am a named inventor in the above-identified patent application. I have a doctorate in Biochemistry, and have been involved in the study of hair growth for over 10 years.

2. Although hair growth occurs in all mammals, in my view only a few species are considered in the hair growth art as acceptable models for the analysis of human hair growth modulation. They include the stump-tailed macaque, the fuzzy rat, the androchronogenetic (AGA) mouse, and the Golden Syrian hamster. These animal models have been well characterized and are accepted for the investigation of hair growth modulators, as described in various peer-reviewed, scientific journals. In addition, these models have been utilized in the development of hair growth stimulators (for male pattern baldness) and hair growth inhibitors agents (for hirsutism).

a. Stump-tailed macaque and fuzzy rat -- In an article published in the Annals of the New York Academy of Sciences (Vol. 642:107-124, 1991; copy enclosed), Uno reviews

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I hereby certify under 37 CFR 1.8(a) that this correspondence is being deposited with the United States Postal Service as **first class mail** with sufficient postage on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Sherry L. Knowlton

models for studying hair growth, *in vivo*. Highlighted in this review are the stump-tailed macaque model and fuzzy rat model. In another article titled "Macaque and rodent models for the screening of drugs for stimulating hair growth" (J. Cutaneous Aging and Cosmetic Dermatol. 1:193-204, 1990; copy enclosed), also from Uno's group, animal models that can be used and are appropriate for studying human hair growth are described. The models include the stump-tailed macaque and the fuzzy rat. These models were used in the development of the hair growth stimulator minoxidil (Rogaine) - the only hair growth drug approved by the Food and Drug Administration ("FDA"). The macaque model is unique in that these animals display post-pubertal, frontal hair loss similar to that observed in human, male pattern baldness. Similarly, the fuzzy rat model has been used to study hair growth due to the age-dependent onset hair growth characterized by small, vellus hair follicles.

b. AGA mouse -- The AGA mouse model is described in an article published by Arch. Dermatol. Res. (Matias et al., 281:247-253, 1989; copy enclosed). This model takes advantage of a mutation that permits the onset of alopecia in the presence of an androgen. Since baldness produced in the AGA mouse parallels that in androgenic alopecia in humans, the use of this animal model for the screening of hair growth stimulators is proposed.

c. Golden Syrian hamster -- The Golden Syrian hamster, flank organ model of hair growth has been widely used for the *in vivo* evaluation of hair growth modulators. The flank organ is an androgen-dependent, pigmented region located

bilaterally on the dorsal side of each hamster and characterized by dark, coarse hairs. These hairs have been linked to beard hair in the human. In 1983, Kaszynski demonstrated a stimulation of hair growth in the flank organs of female hamsters by subcutaneous testosterone propionate (Br. J. Dermatol. 109:565-569, 1983; copy enclosed). This model has also been used to study the hair growth stimulatory effect of topical FK506 (Yamamoto et al., J. Invest. Dermatol. 102:160-164, 1994; copy enclosed), as well as topical minoxidil (Nuck et al., Arch. Dermatol. 123:59-61, 1987; copy enclosed). Another study has described the flank organ, hair follicle response to continuous testosterone stimulation, and indicated the utility of this model for the specific and quantitative assessment of androgenic and antiandrogenic substances on hair growth with particular relevance to hirsutism (Lucky et al., J. Invest. Dermatol. 86:83-86, 1986; copy enclosed). The Golden Syrian hamster model has also been extensively used for hair growth reduction. See Lucky et al., J. Invest. Dermatol. 86:83-86, 1986 (copy enclosed), and Kaszynski, Br. J. Dermatol. 109:565-569, 1983 (copy enclosed), and also the patents described in the Background section of the present application (copies previously provided).

3. In humans, facial and body hair growth is stimulated by androgenic hormones. In contrast, scalp hair growth is not stimulated by androgenic hormones, and in fact, androgenic hormones are in part responsible for male pattern baldness in men genetically susceptible to baldness. See the discuss of androgen-stimulated hair growth and hair growth that

is not androgen-stimulated in The Biology of Hair, F.J.G. Ebling, Dermatologic Clinics, Hair Disorders, 467-481, A.D.J. Mitchell and E.A. Krull, Eds., W.B. Saunders Company, Philadelphia, PA (1987) (copy enclosed).

4. We used the Golden Syrian hamster flank organ model for testing compounds in connection with this application. The model was used to evaluate the effect of various non-steroidal suppressors of angiogenesis on the androgen-stimulated hair growth on the flank organ of the Golden Syrian hamster (see pages 9-12 of the application). Mycophenolic acid was among the suppressors tested, and we found that a composition containing 10% mycophenolic acid reduced hair growth by 65% ± 8%. Based on these results, and on the acceptance of the Golden Syrian hamster assay as a suitable model for human hair growth, a person of ordinary skill in the art would understand that mycophenolic acid would reduce androgen-stimulated hair growth in humans. Moreover, a person of ordinary skill in the art would expect a suppressor of angiogenesis to have the same effect on hair growth that is not androgen-stimulated because the apparent mechanism by which suppressors of angiogenesis act (suppression of angiogenesis) would not be expected to vary depending on whether hair growth is androgen-stimulated. As a result, mycophenolic acid should also reduce hair growth in humans that is not androgen-stimulated.

5. I have reviewed JP 07112929 ("JP '923"). JP '923 concerns finding a cure for baldness in humans and reports that mechophenol acid (mycophenolic acid) can be used to stimulate

hair growth. Mechophenol acid was tested in the assay described on page 8 and was found to accelerate hair growth in rabbits. JP '923 also says the "same hair-growth acceleration effect was observed when tested on mice, rats, dogs, cats, horses, and humans," although it does not appear from the article that any actual testing was conducted to support this statement.

6. To my knowledge no hair growth in rabbits is androgen-stimulated. Moreover, it is clear to me that any testing reported in JP '923 was not hair growth that is androgen-stimulated, because hair growth from the scalp in humans is not androgen-stimulated and JP '923 concerns finding a cure for baldness.

7. The rabbit model described in JP '923 has not been established in the art as an acceptable model for human hair growth modulation. As a result, even if the rabbit model test results reported in JP '923 are accurate, the results do not establish that analogous results would be achieved in humans.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that those statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under section 1001 of Title 18 of the United

States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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March 20, 1998

Date

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